

3/9/50

Marcus -

From the two letters that I wrote you over the week-end, you must surmise that I had four completely different ball. The week-end brought the conclusion of nearly two months of "getting closer and closer" to a realization of the nature of the changes going on at Metabol loci. I have been writing up the various experiments and, of course, doing a lot of thinking in the process. I feel you should have a more orderly presentation of the evolution of events in this process rather than the hodge-podge letters that you received over the week-end. It will help to understand why the results came as they did.

In the first place, examination of the behavior of *h*, at new loci, and of the c-mi mutants loci, it becomes apparent that the ^{patterning} mutations of c-mi, or of any Metabol locus giving a pheno-type expression, was a reflection of the relative frequency of one kind of consequence of a

primary event. This primary event was the important consideration for from it one could derive the real nature of the origin of nucleic acid, their behavior in developmental processes and the factors responsible for the primary event leading to expression of changes in phenotypes.

Studies of the C-m loci made it completely obvious that it was a D locus situated at or close to the substance in cleavage & responsible for the "C few" action. Studies of transposition of D nucleic acid to D locus to introduce into this location from another position in the nucleus. The obvious conclusion was drawn: the presence of D at C inhibits the action of the C locus making it a C phenotype. - The e phenotype was known to be present of a locus had a deficiency of the C locus. Evidence for this was obtained in earlier studies. Therefor, no difficulty was encountered in making the inference

will reflect to what has occurred at the C locus. The question that we of primary importance over this. That is a Ds locus; What is it composed of? Why does it inhibit the action of C? What happens when c-mi inhibits to C? What is the nature of the mutation process? What is Ac? Why does it control c-mi (and Ds and C_{46.2} and Ds_{m1})?

What is its ^{natural} composition? Is it a "genus"? Is Ds a "genus"?

The study of Ds, at any position in class 9, of c-mi may Ac gave the clue to the nature of the action going on at all these loci, that is, the primary agent responsible for all these changes is definitely Ac, Ds and c-mi. This action was obviously one that could result in (1) disease processes (2) translocators, with one position of markers at Ds, c-mi or Ac; (3) translocators ^{independently} that were reflections of the events that also were giving rise to (1) and (2). It was also determined that the three processes leading to changes at Ac, Ds, c-mi, C_{46.2} and Ds_{m1}

occur at all three loci at one time in development
In other words, some change in the nucleus does
occur that affects all of these loci and they
all respond to this changed condition in the nucleus.

As far as can be observed, only the Ac controlled
mutable loci were being affected by this change
in the nucleus, that is: Ac, Ds, c-m₁, c-m₂ and t-m₁.
Now what the other mutable loci in the epigenetics. What
other loci being affected? Now, where are they located?
These latter questions I can not answer now but I am
sure that other loci are affected also. They will be
found, I suspect, if the right approach is made. I shall
return to this point later.

Study of the Ac controlled mutable loci showed
an important effect. This is, the time when the
physiological change in the nucleus occurs is controlled
by the dosage of the Ac locus. This was no question of
this. The Ac locus determines when the primary

events were going to occur in the nucleus that
 would affect not only the but all the loci that it
 controlled. What was the controlling? Is the
 control of ^{in terms of} events in the nucleus a reflection of similar
 events that are occurring in nuclei regularly during
^{but} development, ~~or~~ in the case A (and D) the
 event is changed in its timing by some alteration
 that occurs at the moment + the locus? If so, where
 are the + the locus? What part of the chromosome contains
 + the and + D locus? Do ^{the parts + the any + the} features in controlling
 when certain genes will be active in development
 and when other genes will be inhibitory in action so these
 products will not be made? Is the development of
 an organism in an orderly fashion controlled by a
 number of + the and + D loci that affect specific genes
 in the chromatin in each case, controlling when they
 will act and how effectively they will act? What
 would have to consider such a hypothesis?

To appreciate what this controllable group of genes might be, it is necessary to consider what has been found out about the nature of the event that is controlled by Ac. As stated above, it is known that the dosage of Ac is a primary factor in controlling the time when events will occur. It does all Ac controlled loci. One factor in this pattern of variation (changes at mutant loci) is controlled by the presence of the Ac locus. ^{At present no changes in the physical constitution of the nucleus itself have been observed.} It affects ~~itself~~ and all the loci it controls at ^{at} certain specific times in development. This change that occurs to all of these loci can be investigated. This investigation has revealed that the kind of change occurring at these various times to all of these loci has a common factor. The nature of this factor requires consideration. Before discussing this factor, it is necessary to subdivide the Ac controlled mutant loci into two groups - Ds and its derivatives which arise from transpositions of one original Ds locus, and the two

related c-w₂ and D₄-m₁ loci. (7)

I. The D₄ locus and its derivatives.

The D₄ loci are first discerned at the D₄-D₄ and D₄-^{new}D₄ positions - at the junction of the nucleotide and heterodisulfide regions of cleavage 9. Its transposition has been considered elsewhere and the mode of transposition discussed. The mode of transposition is most important. That it is related to cleavage breakage is obvious in some cases. The most important question regarding the mechanism of transposition is this: (1) Is the transposition mechanism related to a spontaneous break in another position in the cleavage complex or (2) does the cleavage position in the cleavage complex or (2) does the cleavage position in the D₄ locus, in reference to the position where this cleavage will occur, induce the breakage at another position in the cleavage? If (2) is correct, how does it induce the new breakage that will result in the insertion of D₄ at this position of breakage? Is the primary event occurring at D₄ likely to involve some physical

(r)

change in the nature of the physical structures of the clusters at D? What do we know about localized change in the physical structures of clusters? Do localized change in the physical structures of clusters lead to "breaks events" in the clusters? What localized parts of the clusters are involved in the "breaks events"? What do we know about "breaks events" in general? Since "mutation" at D obviously involves some mechanism that simulates "breaks - fission" events, or discussed in detail previously, the question of the nature of break - fission events becomes of prime significance.

- About break - fission events, we know the following:
- (1) Mechanism of breaking of a cluster is well known to a broken and capable of fusing with other broken ends.
 - (2) The fusion of broken ends is non-specific with respect to polarization.
 - (3) The breaks occur all along the length of the clusters.

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and give the same type of response, when seen they
occur.

One must conclude from this that the Weaker-fusion
mechanism involves some kind of material
in the cleavage that is of the older nature all
along the cleavage and it is this material that is involved
in the weaker-fusion mechanism. Is this material fiber
or non-fiber with respect to what is produced in the cytoplasm
from the action of genes? Is it something between the real
genes? Are the real genes held together in a chain
by this material? If so, is the Weaker-fusion
mechanism at meiosis a reflection of the older
gene substance? If so, then, the modifications
in the appearance and behavior of chromosomes at
meiosis are reflections of what is happening to this
older gene substance. The first modification that
is noted in all organisms is the tremendous elongation of
the cleavage before the division (the con-clusio division).

Wth they ^{on} elongates of the inter-filar substance - that is, the substance in the cleavage plane is capable of the breaking-fusion phenomena? Or this refers to when equal crossing-over between the few because crossing-over is a mechanism breaking phenomena? Or this not indicated in such organisms as *Neurospora* where the growth of the cleavage is enormous up to the depletion stage? Or the cytoplasm does the cross-over places? At some locality in *Neurospora*? Or the cleavage is sure locality in *Neurospora*? His latter point seems indicated in maize where the obscure says that the kernel is much reduced from germination to death. In *Neurospora*, likewise, it can not be merely spermatogonium. If the long-horn cleavage it can not be merely spermatogonium. If a ^{the} reduction in the volume of the cleavage along with the spermatogonium process. In other words, following crossing-over, there is no longer any need for this extra inter-filar substance.

(11)

It disappears in a hurry. It seems clear, then, that the enormous growth of the chromosomes before division is an expression of the negative part of Cessing-over. Cessing-over is a process of metabolism. Whether under ^{any} the ^{surface} is the chromosome capable of undergoing the Webov-Fischer-Biggs type. As the cytoplasmic bodies studies show, this substance is all along the chromosomes, and it is the mass kind of substance. It is not the true gene that lies ⁱⁿ the nucleolus in the nucleoplasm, but the surface substance.

This last statement can be appreciated if one remembers that formaldehyde has ^{been} ^{shown} to cause the nucleolus not capable of being separated by crossing-over. However, the original formulation ^{now} implies gene and surface substances. The gene, it seems in the Cytokinesis process, is then that substance of the chromosome which can not be subdivided.

(12)

types), ^{or complex} (1), ^{or complex} (2), ^{or complex} (3). It may be quite complex in its activity but not necessarily analyzed by the class - class techniques or the ^{or complex} (3) techniques. No action must be analyzed by ^{or complex} (3) unless.

This method we will return to.

To summarize, we have come to the conclusion that the "true" genes are separated from the others by a switch that is not like the true genes that is ^{switch} ~~not~~ different. It has ^{some} common properties ^{and} capacity to change its length during metabolic cycles, to undergo ^{some} changes that is non-specific.

How can we determine the nature of this ^{non-specific} substances? What kind of material is it? There are several ways of attacking this problem. The obvious direction for this study is to determine the various factors of change in the element on (1) class - class and (2) ^{or complex} (3) phenomena, however precluded.

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This latter direction of attack is twice if the most important because if the inter-cellular substance is the only substance capable of breaking-fusion. However, they all breakage fusions events are reflections of cleavage in this substance. What kind of events bring about breakage and fusion?

(1). X-rays. There must be breakage and fusion. X-ray produce deeply irregulars of the nuclear acids. Through nuclear action (oxidative action) the inter-cellular substance is cleaved. It becomes sticky or a coagulum. Thus, stickiness may be the primary consequence of X-ray. The extent to the cleavages depends upon how the stuck inter-cellular substance will be affected by cleavage number. If in a cleavage - at one locus or at 2 closely associated loci in the cleavage, or in two anti- cleavages at one locus or near to one another in the other cleavages, a variety of changes will occur: absence of a part but; hour-glass, wrinkles, etc.

- (2). Chæræt heat shock - like x-rays for genes.
- (3). Acaplon, X-rays
- (4). U.V. light
- (5). Crosses - cross.
- (6) The sticky gene in *Musca*.
- (7) The Ac-Ds element in *Musca*
- (8). The so-called "normal" hairy ovaries *Drosophila*
(This is most important and appears a species
character. It is not true normal Crossley sex)
- (9) Some of the "positer effect" loci in *Drosophila* (probable).
- (10) The navigator gene in *Cleotis* - a positer effect
- (11) The " " by H.H. Smith - Bridges at screens
Acaplon.
- (12) Temperature - cold heat shock in *Tribolium*, *Pain*, etc.
Heat " in many organisms.
- (13) The "knuts" in *Drosophila* - Bridges, August 1925 paper
+ Stevens Crossley - own paper 1936.
- (14) The effect of muscles in *Drosophila* on Crossley, one in
which not having the muscles are on the cleavers have the muscles

(15) the two-breakers - more effects in second phase.

(15)

If all of the conditions listed above involve linkage and favor them they involve this ^{change in} inter-focal distance between the few, according to our hypothesis. How can we analyze this list of phenomena to find this common factor?

Possibly the easiest way of proceeding to examine leading to a correlation is to examine the D-A story and show how completely the phenotypic changes occur with D-A can be correlated with the "positive-effect" phenotypes in Drosophila. They are certainly the key genes in the two organisms. Second, the mutations occurring at D & A may be considered. The minor occurring at D & A may be considered. These are events associated with a linkage-fusion phenomenon occurring at specific loci. Since the Drosophila positive effect and mutable loci in many ways are equivalent to the ^{some common association with mutable loci} some phenomena, one can then examine the linkage disequilibrium Drosophila on the effecting the "positive effects" and correlate it with what is known about them ^{mainly} and also powers.

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There appears to a complete correspondence in the nature of the reflexes in those latter organisms case in Drosophila.

The Dr-Re story can be given briefly as it has been presented previously in detail. We can divide this group into 2 sections - I. The Ds locus that has been studied for behavior at Ds-flavocut: (1) The nature of the primary event (at Ds) (2) The consequence of this event: a). Deciduous flies either at the Ds locus; b) translocates with 1 allele at Ds; c) translocates and the mechanism of the change of its C-mi locus; d) the event occurring at c-mi (Same as at Ds); e) the nature of the event leading to the C phenotype.

This facts have been considered elsewhere. They may be summarized briefly: Both Ds and c-mi behave exactly alike. Both show the same memory events and both change in constitution (states) in the same way. By analysis between Ds and c-mi, this behavior becomes different; i.e., the hypothesis that c-mi does not have translocates of Ds has been confirmed. The similarity in the behavior of Ds-flavocut and c-mi is uncontroversial. c-mi is a true mutable locus just as Ds-e, and any other existing mutant locus.

State characteristics
by frequent deletion formatters T abl 1.

Events occurring at 2 extreme states of Ds + C - m1

State characterized by few deletions.

1) Deletor
formatters

2) Insertions

Breadth Ds > C - m1

3) Insertions
of Ds.

4) Insert Ds.
no change in diversity.

5) Deficiency of loci
specific to Ds.
Ds lost at reuniting

6) Very few
deletions to Ds.
Ds present.

7) Most of insert.
with same AC
constitutives.

Ds	C - m1	Ds	C - m1
very frequent = \Rightarrow frequent	very frequent few C \rightarrow C mutations	very infrequent	very infrequent high rate of $C \rightarrow C$ mutations
relatively frequent	rather frequent	some occur.	some occur.
some	some. Accompanied by C \rightarrow C mutations	not fitting well enough:	not fitting well enough:
some	some. Accompanied by C \rightarrow C mutations	Frequent	Frequent. Accompanied by C \rightarrow C mutations.
frequent	not fitting well enough	not fitting well enough.	not fitting well enough.
about 1/10 as frequent as 5)	—	—	—
same = same	= same = same		

When $c \rightarrow m_1$ mutates to C, the Ds - types ~~weird~~⁽¹⁷⁾ completely loses its C locus. The C locus is stable in its behavior thereafter. It has lost the Ds activity completely.

Knowing that Ds loci may be removed by the pricess rebarcer, it may be concluded that the $c \rightarrow C$ mutations are when the Ds material leaves the position adjacent to C. The c plasmids also when the Ds material ~~was inserted~~^{now in the position} adjacent to a normal C. It inhibits the action of the C locus at its normal C. It inhibits the action of the C locus at its normal C. When the Ds locus removes this of action in the nucleus, when the Ds locus is removed, inhibiting close + the C gene acts in the nucleus.

What is this Ds locus? What material does it contain? This can be answered from the previous considerations. Ds may be composed of the ^{type} intergenic material and not be a true gene composed of the intergenic material ^{in it} or certain telomeric elements. It is simplest that it is knob structure, situated at this position. The reason for this interpretation will become apparent as we continue the discussion. At present, it would be well to indicate the relationship of $c \rightarrow m_1$ to position effect in Drosophila. The whole

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in *Drosophila* may be used to illustrate the heredity.

When the type of + up to & including the 3rd band is translocated to the center heterochromatin, say of chromosome \overline{IV} , a white phenotype may appear either "homozygous condition, when mottled, or in combination of \times color & whether are the mosaics. "Mutations" to $^{+w}$ may occur, for others, for others; for others, a分明 type recessive seen. They eyes are abnormal in development giving a mottled appearance. That this is due to the association with the heterochromatin \overline{IV} is more clear by + rays which move the genes, including 3rd, to euchromatic positions. Some of these recessives are accompanied by complete conversion to $^{+w}$. Others give mosaics are the (all colors being equal) amount, depends on the position where the gene is inserted (the farther from the centromere, following removal to a new chrom., the easier the event leading to new color occurs). It is something in the heterochromatin of the center of \overline{IV} that affects the behavior of the $^{+w}$ locus making it behave differently with different cases of origin.

(1) New mutation to $^{+w}$; (2) $^{+w}$ or loss of $^{+w}$ mutation to white often accompanied by irregular forest development.

expenses. Moreover it is
likely to be more expensive.

These cases are exactly like the C. M., but: vulnerability of
the + reaction when occurs to foreign heterostimulation +
means from inhibition or change is the action that leads to
losses expenses & even major development of the ego that
occurs at specific times in development. Are the same kinds
of primary events occurring in Mayo + Dorothea in their
cases? What changes are occurring at the +^w locus in Dorothea?
When heterostimulation to heterostimulation? As there change is
the +^w locus or in the adjacent heterostimulation? The
latter all power to change in the heterostimulation and not
in the gene itself (+^w) adjacent to the heterostimulation.
But if this occurs is (1) The effect of the Y chromosome = to delay the
(2) The effect of the +^w locus = to make the heterostimulation occur
time when change will occur at the +^w locus, (3) The
effect of low or high temperature on the time and
thus the opposite frequency of occurs. Both of these where if
temperature affects heterostimulation. (Parlejel, et.al.)
Temperature affects heterostimulation, ^{causes} resulting in defensive
behavior, making it sticky and result in defensive
behaviors and fears. The central heterostimulation, stimulus,
controls the time when occurs will occur at the heterostimulation +^w

locus and the leaves that occur ^(and) resolute, ~~gradually~~, (20)
the events occur at a \sim u_1 , that is, loss of tree

substituted ^{substance} or ~~leaves~~ in the leaves producing
newer & different. The tree ~~and~~ ^{of the part} is under the
control of the latter elements just as the trees of events
are controlled by the new leaves of the latter elements
disturbances in the ~~Reef~~ reflects with Dr. It would appear

that latter elements is involved in both of cases in
controlling the events that occur at suitable loci. It is
obvious, in the case of u_1 & $c u_1$, that these events lead to
decreased leafage. We have shown above that decrease
leafage involves the latter ^{leaf} substance. Hence, we
can conclude that the material composition u_1 is either
dead, either ^{or} latter elements out of place or that it is other.

~~material causing the latter leaf material to become disorganized~~
~~at the time when it is not proper for this location, latter leaf~~
~~substance out of place and that change in this latter substance~~
~~leading to stickiness at this position is the consequence of any~~
~~other process, affecting all ^{newer} materials and more leaves~~

development that is under the control of the Rabb and
Centri hetero electrons. The Rabb + the ^{extra} hetero electrons
substance as the organizers of the theory of cause at
water film substance that will lead to vulnerability
of film action at various position in the elements &
will now control the means of seed vulnerability. In
this way, ~~the~~^{this view} few can set up the right time & the
non-regarded as vulnerable. It in this situation in that the
controlling oxygen atoms, Rabb + water hetero electrons
that will be reflected by altering the action of the
water film substance and therefore giving rise to what
appear as "metals" of a suitable form. Hence,
any condition that changes the hetero electrons concerned
will be reflected in the ^{action} of the film.
D_a, is therefore, substance that normally made molecules at
a time other than ~~when~~ the normal water film substance at C.
During environmental development, it is in the state that vulnerable
action of its C. Alteration ^{in the time} of action of D_a will occur when

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Δc is present because Δc is hetero deviations that
has been affected by induced Raefects. The same
relationships holds for Δt and a .